LRRK2 modifies alpha-syn pathology and spread in mouse models and human neurons.

Public Summary:

Progressive aggregation of the protein alpha-synuclein (alpha-syn) and loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) are key histopathological hallmarks of Parkinson's disease (PD). Accruing evidence suggests that alpha-syn pathology can propagate through neuronal circuits in the brain, contributing to the progressive nature of the disease. Thus, it is therapeutically pertinent to identify modifiers of alpha-syn transmission and aggregation as potential targets to slow down disease progression. A growing number of genetic mutations and risk factors has been identified in studies of familial and sporadic forms of PD. However, how these genes affect alpha-syn aggregation and pathological transmission, and whether they can be targeted for therapeutic interventions, remains unclear. We performed a targeted genetic screen of risk genes associated with PD and parkinsonism for modifiers of alpha-syn aggregation, using an alpha-syn preformed-fibril (PFF) induction assay. We found that decreased expression of Lrrk2 and Gba modulated alpha-syn aggregation in mouse primary neurons. Conversely, alpha-syn aggregation increased in primary neurons from mice expressing the PD-linked LRRK2 G2019S mutation. In vivo, using LRRK2 G2019S transgenic mice, we observed acceleration of alpha-syn aggregation and degeneration of dopaminergic neurons in the SNpc, exacerbated degeneration-associated neuroinflammation and behavioral deficits. To validate our findings in a human context, we established a novel human alpha-syn transmission model using induced pluripotent stem cell (iPS)-derived neurons (iNs), where human alpha-syn PFFs triggered aggregation of endogenous alpha-syn in a time-dependent manner. In PD subject-derived iNs, the G2019S mutation enhanced alpha-syn aggregation, whereas loss of LRRK2 decreased aggregation. Collectively, these findings establish a strong interaction between the PD risk gene LRRK2 and alpha-syn transmission across mouse and human models. Since clinical trials of LRRK2 inhibitors in PD are currently underway, our findings raise the possibility that these may be effective in PD broadly, beyond cases caused by LRRK2 mutations.

Scientific Abstract:

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